

**SENSOR FOR TRANSCUTANEOUS MEASUREMENT
OF VASCULAR ACCESS BLOOD FLOW**

CROSS REFERENCE TO RELATED APPLICATION(S)

[0001] This application is a continuation-in-part of Application Ser. No. 09/750,076, filed December 29, 2000; and a continuation-in-part of Application No. 09/771,596, filed January 30, 2001, which is a continuation of Application No. 09/244,756, filed February 5, 1999, now U.S. Patent No. 6,181,958, which claims the benefit of Provisional Application No. 60/073,784, filed February 5, 1998), all of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

[0001] The present invention relates to apparatus for non-invasively measuring one or more blood parameters. More specifically, the invention relates to apparatus for the transcutaneous measurement of vascular access blood flow ("TQA") that is capable of generating accurate TQA measurements, even when the volume of access being measured is extremely small in size or extremely deep or when the access is of varying nature, such as a synthetic or native fistula. Further, it is possible to infer additional information about the access area, such as collateral veins or competing vessels.

BACKGROUND OF THE INVENTION

[0002] Access blood flow for hemodialysis patients can now be measured non-invasively through a novel photo-optic transcutaneous technique as described in co-pending Application Ser. No. 09/750,122, filed December 29, 2000 (which is

incorporated herein by reference in its entirety), using a transcutaneous TQA sensor as disclosed in Application Ser. No. 09/750,076, filed December 29, 2000 (which is also incorporated herein by reference in its entirety), and more particularly, the transcutaneous TQA sensor described in connection with FIGURES 2-6 thereof (hereinafter, "the prior art linear sensor").

[0003] With reference to FIGURES 1, 2, and 2A, the prior art linear sensor 10 includes two light emitting sources (emitters) 12a and 12b, preferably light emitting diodes (LEDs) of specific wavelengths, and two complementary silicon photodiode detectors 14a and 14b alternatingly arranged in a straight line at identical intervals to form three LED/detector pairs with identical separations between the members of each pair, for the purpose of measuring the bulk absorptivity (α) of the volume immediately surrounding and including the access site A, and the absorptivity (α_o) of the tissue itself. The LEDs preferably emit light at a wavelength of 805 nm - 880 nm, because it is near the known isobestic wavelength for hemoglobin, is commercially available, and has been shown to be effective in the optical determination of whole blood parameters such as hematocrit and oxygen saturation.

[0004] The technique is accomplished by directly placing the prior art linear sensor 10 on the skin of a patient with the aligned emitters 12a and 12b and detectors 14a and 14b perpendicular to the vascular access site A, and measuring the back-scattered light from a turbid tissue sample to determine the percentage change in hematocrit ΔH as a bolus of saline passes through the access vessel.

[0005] When the prior art linear sensor 10 is placed on the surface of the skin, each LED 12a and 12b illuminates a volume of tissue T, and a small fraction of the light absorbed and back-scattered by the tissue and red blood cells is detected by its adjacent photodetector 14a or 14b, which generates a detection signal. When the volume of tissue illuminated includes all or even part of the access A, the resultant α value includes information about both the surrounding tissue T and the access itself. In order to resolve the signal due to blood flowing within the access A from that due to the surrounding tissues T, the prior art linear sensor 10 illuminates adjacent tissue regions T on either side of the access A. Values of α_0 for tissue regions T not containing the access A are then used to normalize the signal, thus providing a baseline from which relative changes can be assessed in access hematocrit in the access blood flowing directly under the skin. The intensity of the signal produced by each photodetector 14A or 14B is proportional to the total absorption and scattering within a given volume of tissue between each detector 14a or 14B and its adjacent LED 12a or 12b. During saline dilution, only the hematocrit inside the access A varies, and the detected signal changes are solely dependent upon the optical property changes within the small volume of access viewed by the sensor 10.

[0006] By correcting the signal in the volume containing the access A with the average reference signal in the volumes without access, the sensor 10 provides a signal solely dependent on the hematocrit flowing in the access. Then, traditional Ficke principle mathematics can be used to calculate the blood flow rate using the following equation:

$$Q_a = \frac{V}{\int \frac{\Delta H(t)}{H_a} dt}$$

[0007] For a given separation between LED and photodiode in the sensor 10, the volume of tissue illuminated and viewed by the prior art linear sensor 10 is relatively constant and the signal-to-noise ratio of this technique depends on the volume of access included inside the tissue volume. When the volume of access included inside the tissue volume is small enough due to extremely small size or excessive depth, the signal-to-noise ratio falls to a level that would not generate accurate measurement results. It would accordingly be desirable to improve the signal-to-noise ratio so that accurate measurements can be taken even when the access is extremely small or very deep.

[0008] According to W. Cui ("Photon Diffusion Theory and Noninvasive Tissue Optical Property Measurement," PhD. Thesis, Biomedical Engineering Department, Rensselaer Polytechnic Institute (1990)), the principle path of diffused photons in a turbid medium is in the gradient direction of the photon density distribution, which is perpendicular to the contour surfaces. Along this direction, photons consistently travel all the way from the LED to the detector in a curved path. In a later study, W. Cui *et al.* ("Experimental Study of Migration Depth for the Photons Measured at Sample Surface," *SPIE*, Vol. 1431, pp 180-191 (1991)) further showed that the photon flux path from LED to detector has a "banana" shape that reaches deepest into the tissue at the mid-portion of the "banana." More significantly, in this "banana"-shaped photon path, there is a region in the middle between LED and detector near the

tissue surface that is totally outside the detected photon flux path. This means that anything in this region will not interact with the photons that reach the detector and will never be “seen” by the detector. This finding was verified by S. Feng *et al.* (“Monte Carlo Simulations of Photon Migration Path Distributions in Multiple Scattering Media,” *SPIE*, Vol. 1888, pp 78-89 (1993)), using both analytical perturbative diffusion theory and Monte Carlo simulations. This phenomenon also explains the clinical observations that with a visually observable shallow graft, no significant difference in α is detected with the injection of a saline bolus.

[0009] The configuration of the prior art linear sensor 10 allows it (or more precisely, the aligned LEDs 12a and 12b and the detectors 14a and 14b) to be perpendicular to the access A and the photon flux F to travel across the access to generate an illuminated volume of access within the illuminated tissue volume, as shown in FIGURES 1 and 2. For a graft in the center of the photon flux path F, the volume of the access viewed by the prior art linear sensor 10 is limited to the cross-section of the graft and the photon flux path F as indicated by FIGURES 1 and 2. For a graft that is nearly out of the photon flux path F (because it is too shallow, as shown in FIGURE 2A, or too deep) the volume of access “seen” by the prior art linear sensor 10 is so small that the signal-to-noise ratio is too low to give accurate measurements.

[00010] It is to the solution of this and other problems that the present invention is directed.

BRIEF SUMMARY OF THE INVENTION

[00011] It is therefore a primary object of the present invention to provide apparatus for non-invasively measuring one or more blood parameters associated with a vascular access, even when the volume of access being measured is extremely small in size or extremely deep.

[00012] It is another object of the present invention to provide a sensor for transcutaneous TQA measurement that is capable of generating accurate TQA measurements, even when the volume of access being measured is extremely small in size or extremely deep.

[00013] This and other objects of the invention is achieved by the provision of an optical sensor including two pairs of complementary emitter and detector elements, wherein the pairs of emitter and detector elements define two lines at right angles to each other, for the purpose of measuring the bulk absorptivity (α) of the volume immediately surrounding and including the access site, and the absorptivity (α_0) of the tissue itself.

[00014] In one aspect of the invention, one of the pairs lies to one side of the line defined by the other of the pairs, such that the two pairs of emitter and detector elements form a "T" shape.

[00015] In another aspect of the invention, each pair of emitter and detector elements comprises an LED of specific wavelength and a complementary photodetector. A

wavelength of 805 nm - 880 nm, which is near the known isobestic wavelength for hemoglobin, is used.

BRIEF DESCRIPTION OF THE DRAWINGS

[00016] FIGURE 1 is a bottom diagrammatic view of a prior art TQA sensor in place over a vascular access site.

[00017] FIGURE 2 is a cross-sectional view taken along line 2-2 of FIGURE 1.

[00018] FIGURE 2A is a cross-sectional view of a prior art TQA sensor in place over a very shallow vascular access site.

[00019] FIGURE 3 is a bottom plan view of a TQA sensor in accordance with the present invention.

[00020] FIGURE 4 is a top plan view of the TQA sensor of FIGURE 3.

[00021] FIGURE 5 is a side elevational view of the TQA sensor of FIGURE 3.

[00022] FIGURE 6 is a cross-sectional view taken along line 6-6 of FIGURE 3.

[00023] FIGURE 6A is enlarged view of the area 6A of FIGURE 6.

[00024] FIGURE 7 is a cross-sectional view taken along line 7-7 of FIGURE 3.

[00025] FIGURE 8 is a top plan view of the substrate of the TQA sensor of FIGURE 3.

[00026] FIGURE 9 is bottom plan view of the substrate of FIGURE 8 and the circuitry thereon.

[00027] FIGURE 10 is a bottom diagrammatic view of the TQA sensor of FIGURE 3, in place over a vascular access site.

[00028] FIGURE 11 is a cross-sectional view taken along line 11-11 of FIGURE 10.

[00029] FIGURE 12 is a cross-sectional view taken along line 12-12 of FIGURE 10.

[00030] FIGURE 13 is a graph comparing the signal change detected by the TQA sensor of FIGURE 3 to the signal change detected by the prior art TQA sensor of FIGURE 1.

DETAILED DESCRIPTION OF THE INVENTION

[00031] In describing preferred embodiments of the present invention illustrated in the drawings, specific terminology is employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology so selected, and it is to be understood that each specific element includes all technical equivalents that operate in a similar manner to accomplish a similar purpose.

[00032] Referring now to FIGURES 3-7, there is shown a sensor 100 for the transcutaneous measurement of vascular access blood flow in a hemodialysis shunt or fistula A in accordance with the present invention. The sensor 100 comprises a body 102 having upper and lower surfaces 102a and 102b, a surrounding exterior cover

104, a first emitter/detector element pair 106a-106b set into the exterior cover 104 on the lower surface of the body 102, and a second emitter/detector element pair 108a-108b set into the exterior cover 104 on the lower surface of the body 102. Preferably, the emitter elements 106a and 108a are LEDs of specific wavelengths, preferably, a wavelength of 805 nm - 880 nm; and preferably, the detector elements 106b and 108b are silicon photodiode detectors that are complementary to the LEDs.

[00033] The pairs of emitter and detector elements 106a-106b and 108a-108b define two lines L1 and L2 at right angles to each other. One of the pairs lies to one side of the line defined by the other of the pairs, such that the lines L1 and L2 defined by the two emitter/detector element pairs 106a-106b and 108a-108b form a "T" shape. The emitter/detector element pair 106a-106b that defines the cross-bar of the "T" shape (the "sensing" emitter/detector element pair) is placed over and parallel to the access A and measures the bulk absorptivity α of the volume of the access site and the volume immediately below the access site. The emitter/detector element pair 108a-108b that defines the stem of the "T" shape (the "normalizing" emitter/detector element pair) thus is placed to one side of and perpendicular to the access A and measures the absorptivity α_0 of a tissue region T that does not contain the access A.

[00034] It does not matter which element of the normalizing emitter/detector element pair 108a-108b is the element that is closer to the sensing emitter/detector element pair 106a-106b, as long as the geometry and spacing between the elements of the individual pairs are maintained. When the geometry and spacing between the elements of the individual pairs are maintained, the light path is symmetric and the

placement of the emitter element and the detector element in each pair can be reversed with impunity.

[00035] With the “T” shape of the sensor 100, the sensing emitter/detector element pair 106a-106b is parallel to the access A and the photon flux path F is along the access line as shown in FIGURES 10-12. For a graft within a normal photon flux path, the volume of access viewed by the detector element 106b of the sensing emitter/detector element pair 106a-106b is larger than the volume viewed by the detectors 14a and 14b in the prior art linear sensor 10 of FIGURES 1, 2, and 2A. The sensor 100 hence increases the detection limit and sensitivity of the measurements, as shown in FIGURE 13. For those grafts that are nearly undetectable with the prior art linear sensor 10 configuration of FIGURES 1, 2, and 2A, the advantage of the “T”-shaped sensor 100 in accordance with the present invention is more significant, because the volume of access viewed by the detector is much larger at both ends of the “banana” shaped photon flux path F, as shown in FIGURE 9. This increase in volume of access viewed makes the “T”-shaped sensor 100 in accordance with the present invention less sensitive to the depth of the graft within its scope.

[00036] As shown in FIGURES 3, 6, and 7, the exterior cover 104 is provided with apertures 110 in its lower surface (the surface that in use faces the access site) for receiving the emitters 106a and 108a and the detectors 106b and 108b. The apertures 110 are sized so that the emitters 106a and 108a and the detectors 106b and 108b lie flush with the lower surface of the body 102 (that is, the surface that contacts the skin). The upper surface of the exterior cover 104 may have a depression formed

therein for manufacturing purposes. Alignment pins are used to hold the emitters 106a and 108a and detectors 106b and 108b on position during molding and leave the depressions after the sensor is removed from the mold.

[00037] Preferably, the exterior cover 104 is provided with markers 114 visible from the upper surface for guiding placement of the sensor 100 over the access. As shown in FIGURES 3-5, these markers 114 can take the form of indentations in the sides of the body 102. As will be appreciated by those of skill in the art, the markers 114 can also take other forms, such as printed or inscribed lines, arrows, or other markings.

[00038] As shown in FIGURES 6 and 6A, the sensor body 102 is a laminate structure comprising a substrate 120 having upper and lower surfaces 120a and 120b, upper and lower conducting layers 130 and 132 overlying the upper and lower surfaces 120a and 120b, respectively, and defining the circuitry of the sensor 100, and a surrounding interior cover 140. As discussed in greater detail below, and as shown in FIGURE 6A, there may also be outer upper and lower adhesive layers (not shown) between the upper and lower conducting layers and the interior cover 140 and inner upper and lower adhesive layers between the upper and lower surfaces 120a and 120b of the substrate 120 and the upper and lower conducting layers.

[00039] As shown in FIGURE 9, the circuitry 170 associated with the emitter/detector element pairs 106a-106b and 108a-108b can be provided as a printed circuit on the upper and lower surfaces 120a and 120b of the substrate 120. The interior cover 140 over the upper conducting layer 130 has access holes therethrough (not shown) at the connector fingers 170a of the circuitry 170, and at the component pads 170b of the

circuitry 170. Corresponding holes 172 are provided (e.g., by drilling) through the interior cover 140 to permit the emitter elements 106a and 108a and the detector elements 106b and 108b to be soldered to their respective component pads 170b.

[00040] The substrate 120 is made of a material, such as a polyimide or polyimide-containing film, that is flexible enough to conform to the contours of the underlying tissue but rigid enough to have body durability. The exterior and interior covers 104 and 140 and the conducting layers 130 and 132 similarly must be flexible enough to conform to the contours of the underlying tissue but rigid enough to have body durability. For example, the interior cover 140 can be a flexible, dry-film, soldermask material, preferably a polyimide or other imide-containing film, which is applied over the substrate 120 and the conducting layers 130 and 132 in a tacky state with heat and vacuum and then oven cured onto the substrate 120 so that it bonds directly with the conductive layers 130 and 132. The purpose of a soldermask material being to encapsulate totally the underlying circuitry to protect it from the intended operating environment, the dry-film soldermask must be thick enough to flow over and around the component pads and traces of the circuitry during lamination. The substrate 120 and the upper and lower conducting layers 130 and 132 can be made of DuPont Pyralux® AP 9222 double-sided, copper-clad laminate, which is an all-polyimide composite of 2.0 mil polyimide film bonded to 2.8 mil 2 oz/ft² copper foil. The interior cover 140 can be made of 2.5 mil DuPont Pyralux® PC1025 photoimageable coverlay, which is a flexible, dry film solder mask consisting of a combination of acrylic, urethane, and imide-based material. The exterior cover 104 preferably is a plastic material such as urethane or silicone, and more particularly, a rubber silicon

with, for example, a thickness of 1 mil. A rubber silicon material with a thickness of 1 mil has a durometer of 30.

[00041] The major consideration in the choice of the material and thickness of the substrate 120, the conducting layers 130 and 132, the interior cover 140, the adhesive (if any), and exterior cover 104 is the total flexibility of the sensor 100. That is, the net flexibility of the sensor 100 must meet the above stated requirements for rigidity. As will be appreciated by those of skill in the art, there are numerous combinations of materials and dimensions that will produce an acceptable flexibility.

[00042] The requirement for an outer upper and lower adhesive layer is dependent upon the composition of the interior cover 140, while the requirement for an inner upper and lower adhesive layer is dependent upon the composition of the substrate 120. For example, certain imide-containing films require an adhesive between the substrate 120 and the upper and lower conducting layers 130 and 132 because they do not incorporate any adhesive in their outer surfaces; while other imide-containing films incorporate a very thin layer of adhesive in their outer surfaces and are homogeneous after they are cured and thus do not require a separate adhesive layer between the substrate 120 and the upper and lower conducting layers 130 and 132. As each adhesive layer (when used) is about 1 mil thick, where it is desired to minimize the thickness of the sensor 100 (for example, to enable the sensor 100 to more easily conform to the surface of the skin where the access site sits near the surface of the skin, or on small arms where a the radius of curvature is tighter, or in general in any application requiring that the sensor 100 be more flexible) it is

preferable to use materials for the substrate 120 and the interior cover 140 that do not require an adhesive.

[00043] The sensor 100 is connected to an associated monitoring system (not shown) by the cable 180. The monitoring system can be a computer including a computer processor and memory, and output means such as a video monitor and printer (not shown).

[00044] As shown in FIGURES 10-12, there are two “banana”-shaped photon flux paths in the tissue seen by the two detectors 106b and 108b: a first (or sensing) photon flux path F1 representing the reflective penetration volume (α) of the sensing emitter element 106a through the access A and the access site tissue as seen by the sensing detector element 106b in the process of determination of the access Hematocrit H; and a second (or normalizing) photon flux path F2 representing the reflective penetration (α_0) of the normalizing emitter element 108a through the non-access site tissue to one side of the access site as seen by the normalizing detector element 108b. The measurements of α and α_0 can then be used to calculate $F\left(\frac{\Delta H}{H}\right)$ in accordance with Equation (13) of Application Ser. No. 09/750,076.

[00045] In order to use indicator dilution techniques to measure vascular access flow rates during routine hemodialysis, the indicator must be injected upstream and its concentration detected downstream in the blood flowing through the vascular access site, as described in co-pending Application Ser. No. 09/750,076. Because the sensor 100 can detect a dilution signal downstream of the venous needle through the skin, a

unique application of indicator dilution principles permits determination of the vascular access flow rate without reversal of the dialysis blood lines. The sensor 100 can be used to carry out the various methods of measuring vascular access blood flow rate, as well as the method for locating accesses and grafts and localizing veins in normal patients, as described in co-pending Application Ser. No. 09/750,122.

[00046] Due to the depth of the access site, in order for the full depth of the access site to be intersected by the first photon flux path F1, the spacing between the centers of the sensing emitter and detector elements 106a and 106b is typically about 16.8 mm. The spacing between the centers of the normalizing emitter and detector elements 108a and 108b also is typically about 16.8 mm. The spacing between the center of the normalizing detector 108b and the line L1 defined by the centers of the sensing emitter/detector element pair 106a-106b is typically about 16.6 mm. However, other separations can be used and may have advantages in controlling depths of penetration avoiding competing structures such as bone.

[00047] Also, an emitter element-detector element separation is required so that the reflectance of the first layer of tissue (a non-blood layer of epithelium) does not further exaggerate a multiple scattering effect, as discussed in U.S. Patent No. 5,499,627, which is incorporated herein by reference in its entirety.

[00048] As indicated above, the emitter elements 106a and 106b are preferably LEDs that emit light at a wavelength of 805 nm - 880 nm, and the detector elements 108a and 108b are silicon photodiodes, and the exterior cover 104 is formed by molding or other means such that the emitter elements 106a and 108a and the detector elements

106b and 108b lie flush with the lower surface of the exterior cover 104, that is, the surface that faces the skin, so that both of the emitter/detector element pairs 106a-106b and 108a-108b lie on the skin.

[00049] Finally, the sensor 100 can be fastened in place using surgical tape. Alternatively, the sensor can be made as a disposable adhesive patch that cannot be recalibrated and used again, as described in Application Ser. No. 09/750,076.

[00050] All other factors remaining the same, when the emitter/detector element pairs 106a-106b and 108a-108b are arranged in a "T" shape in accordance with the present invention, rather than in a linear configuration as in the prior art linear sensor 10 of Application Ser. No. 09/750,076, the volume of access, and thus the signal strength, are significantly improved. With the improvement in signal strength, the "T"-shaped sensor 100 in accordance with the present invention can detect some accesses that could not be identified by the prior art linear sensor 10; and the "T"-shaped sensor 100 in accordance with the present invention can accurately measure accesses that could not be viewed "clearly" by the prior art linear sensor 10. In effect, the "T"-shaped configuration of the sensor 100 in accordance with the present invention gives more accurate measurements to smaller, shallower, and/or deeper accesses.

[00051] As shown in FIGURE 7, *in vitro* experimental results indicate that under the same experimental conditions, the signal change detected by the "T"-shaped sensor 100 in accordance with the present invention is about 40% higher than that detected by the prior art linear sensor 10. The increase in signal strength also increased the overall TQA calculation slope from 894 to 1187.

[00052] Modifications and variations of the above-described embodiments of the present invention are possible, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the appended claims and their equivalents, the invention may be practiced otherwise than as specifically described.

11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000
1001
1002
1003
1004
1005
1006
1007
1008
1009
1010
1011
1012
1013
1014
1015
1016
1017
1018
1019
1020
1021
1022
1023
1024
1025
1026
1027
1028
1029
1030
1031
1032
1033
1034
1035
1036
1037
1038
1039
1040
1041
1042
1043
1044
1045
1046
1047
1048
1049
1050
1051
1052
1053
1054
1055
1056
1057
1058
1059
1060
1061
1062
1063
1064
1065
1066
1067
1068
1069
1070
1071
1072
1073
1074
1075
1076
1077
1078
1079
1080
1081
1082
1083
1084
1085
1086
1087
1088
1089
1090
1091
1092
1093
1094
1095
1096
1097
1098
1099
1100
1101
1102
1103
1104
1105
1106
1107
1108
1109
1110
1111
1112
1113
1114
1115
1116
1117
1118
1119
1120
1121
1122
1123
1124
1125
1126
1127
1128
1129
1130
1131
1132
1133
1134
1135
1136
1137
1138
1139
1140
1141
1142
1143
1144
1145
1146
1147
1148
1149
1150
1151
1152
1153
1154
1155
1156
1157
1158
1159
1160
1161
1162
1163
1164
1165
1166
1167
1168
1169
1170
1171
1172
1173
1174
1175
1176
1177
1178
1179
1180
1181
1182
1183
1184
1185
1186
1187
1188
1189
1190
1191
1192
1193
1194
1195
1196
1197
1198
1199
1200
1201
1202
1203
1204
1205
1206
1207
1208
1209
1210
1211
1212
1213
1214
1215
1216
1217
1218
1219
1220
1221
1222
1223
1224
1225
1226
1227
1228
1229
1230
1231
1232
1233
1234
1235
1236
1237
1238
1239
1240
1241
1242
1243
1244
1245
1246
1247
1248
1249
1250
1251
1252
1253
1254
1255
1256
1257
1258
1259
1260
1261
1262
1263
1264
1265
1266
1267
1268
1269
1270
1271
1272
1273
1274
1275
1276
1277
1278
1279
1280
1281
1282
1283
1284
1285
1286
1287
1288
1289
1290
1291
1292
1293
1294
1295
1296
1297
1298
1299
1300
1301
1302
1303
1304
1305
1306
1307
1308
1309
1310
1311
1312
1313
1314
1315
1316
1317
1318
1319
1320
1321
1322
1323
1324
1325
1326
1327
1328
1329
1330
1331
1332
1333
1334
1335
1336
1337
1338
1339
1340
1341
1342
1343
1344
1345
1346
1347
1348
1349
1350
1351
1352
1353
1354
1355
1356
1357
1358
1359
1360
1361
1362
1363
1364
1365
1366
1367
1368
1369
1370
1371
1372
1373
1374
1375
1376
1377
1378
1379
1380
1381
1382
1383
1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414
1415
1416
1417
1418
1419
1420
1421
1422
1423
1424
1425
1426
1427
1428
1429
1430
1431
1432
1433
1434
1435
1436
1437
1438
1439
1440
1441
1442
1443
1444
1445
1446
1447
1448
1449
1450
1451
1452
1453
1454
1455
1456
1457
1458
1459
1460
1461
1462
1463
1464
1465
1466
1467
1468
1469
1470
1471
1472
1473
1474
1475
1476
1477
1478
1479
1480
1481
1482
1483
1484
1485
1486
1487
1488
1489
1490
1491
1492
1493
1494
1495
1496
1497
1498
1499
1500
1501
1502
1503
1504
1505
1506
1507
1508
1509
1510
1511
1512
1513
1514
1515
1516
1517
1518
1519
1520
1521
1522
1523
1524
1525
1526
1527
1528
1529
1530
1531
1532
1533
1534
1535
1536
1537
1538
1539
1540
1541
1542
1543
1544
1545
1546
1547
1548
1549
1550
1551
1552
1553
1554
1555
1556
1557
1558
1559
1560
1561
1562
1563
1564
1565
1566
1567
1568
1569
1570
1571
1572
1573
1574
1575
1576
1577
1578
1579
1580
1581
1582
1583
1584
1585
1586
1587
1588
1589
1590
1591
1592
1593
1594
1595
1596
1597
1598
1599
1600
1601
1602
1603
1604
1605
1606
1607
1608
1609
1610
1611
1612
1613
1614
1615
1616
1617
1618
1619
1620
1621
1622
1623
1624
1625
1626
1627
1628
1629
1630
1631
1632
1633
1634
1635
1636
1637
1638
1639
1640
1641
1642
1643
1644
1645
1646
1647
1648
1649
1650
1651
1652
1653
1654
1655
1656
1657
1658
1659
1660
1661
1662
1663
1664
1665
1666
1667
1668
1669
1670
1671
1672
1673
1674
1675
1676
1677
1678
1679
1680
1681
1682
1683
1684
1685
1686
1687
1688
1689
1690
1691
1692
1693
1694
1695
1696
1697
1698
1699
1700
1701
1702
1703
1704
1705
1706
1707
1708
1709
1710
1711
1712
1713
1714
1715
1716
1717
1718
1719
1720
1721
1722
1723
1724
1725
1726
1727
1728
1729
1730
1731
1732
1733
1734
1735
1736
1737
1738
1739
1740
1741
1742
1743
1744
1745
1746
1747
1748
1749
1750
1751
1752
1753
1754
1755
1756
1757
1758
1759
1760
1761
1762
1763
1764
1765
1766
1767
1768
1769
1770
1771
1772
1773
1774
1775
1776
1777
1778
1779
1780
1781
1782
1783
1784
1785
1786
1787
1788
1789
1790
1791
1792
1793
1794
1795
1796
1797
1798
1799
1800
1801
1802
1803
1804
1805
1806
1807
1808
1809
1810
1811
1812
1813
1814
1815
1816
1817
1818
1819
1820
1821
1822
1823
1824
1825
1826
1827
1828
1829
1830
1831
1832
1833
1834
1835
1836
1837
1838
1839
1840
1841
1842
1843
1844
1845
1846
1847
1848
1849
1850
1851
1852
1853
1854
1855
1856
1857
1858
1859
1860
1861
1862
1863
1864
1865
1866
1867
1868
1869
1870
1871
1872
1873
1874
1875
1876
1877
1878
1879
1880
1881
1882
1883
1884
1885
1886
1887
1888
1889
1890
1891
1892
1893
1894
1895
1896
1897
1898
1899
1900
1901
1902
1903
1904
1905
1906
1907
1908
1909
1910
1911
1912
1913
1914
1915
1916
1917
1918
1919
1920
1921
1922
1923
1924
1925
1926
1927
1928
1929
1930
1931
1932
1933
1934
1935
1936
1937
1938
1939
1940
1941
1942
1943
1944
1945
1946
1947
1948
1949
1950
1951
1952
1953
1954
1955
1956
1957
1958
1959
1960
1961
1962
1963
1964
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
2026
2027
2028
2029
2030
2031
2032
2033
2034
2035
2036
2037
2038
2039
2040
2041
2042
2043
2044
2045
2046
2047
2048
2049
2050
2051
2052
2053
2054
2055
2056
2057
2058
2059
2060
2061
2062
2063
2064
2065
2066
2067
2068
2069
2070
2071
2072
2073
2074
2075
2076
2077
2078
2079
2080
2081
2082
2083
2084
2085
2086
2087
2088
2089
2090
2091
2092
2093
2094
2095
2096
2097
2098
2099
2100
2101
2102
2103
2104
2105
2106
2107
2108
2109
2110
2111
2112
2113
2114
2115
2116
2117
2118
2119
2120
2121
2122
2123
2124
2125
2126
2127
2128
2129
2130
2131
2132
2133
2134
2135
2136
2137
2138
2139
2140
2141
2142
2143
2144
2145
2146
2147
2148
2149
2150
2151
2152
2153
2154
2155
2156
2157
2158
2159
2160
2161
2162
2163
2164
2165
2166
2167
2168
2169
2170
2171
2172
2173
2174
2175
2176
2177
2178
2179
2180
2181
2182
2183
2184
2185
2186
2187
2188
2189
2190
2191
2192
2193
2194
2195
2196
2197
2198
2199
2200
2201
2202
2203
2204
2205
2206
2207
2208
2209
2210
2211
2212
2213
2214
2215
2216
2217
2218
2219